PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2005/000512	28.02.2005	27.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D417/12, A61K31/496, A61P25/18

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Authorized Officer

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2005/000512

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☑ claims Nos. 31 with respect to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 31 with respect to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,9-11,15,16
	No:	Claims	5-8,12-14,17,18-31
Inventive step (IS)	Yes:	Claims	1-4
	No:	Claims	5-31
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

1. A non-unity objection has been raised during the search stage. The Applicant has paid extra search fees, so that the opinion will be given for the subject-matter of the 3 inventions.

2. Claim 31 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (article 34(4)(a)(i) PCT).

For the assessment of the presently worded claim 31 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such compound for the manufacture of a medicament for a new medical treatment.

Re Item IV.

1. The ISA found multiple inventions (three) in this application, as follow:

Invention 1 (claims: 1-4): Alternative process for the preparation of ziprasidone base,

Invention 2 (claims: 5-21): Alternative process for the preparation of substantially pure ziprasidone base,

Invention 3 (claims 22-31): Alternative process for the preparation of substantially pure ziprasidone hydrochloride, pharmaceutical composition and uses thereof.

2. The International Examination Authority (IEA) fully supports the non-unity objection of the ISA. The 3 inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The present application contains 3 different problems solved by different technical means

which do not share any common technical feature since the ziprasidone compound is already known from the cited documents US-A-4831031 (see column 13, l. 13-17) and US-A-6150366 (see claim 1).

The first proposed problem (first invention) is the provision of an alternative process for the preparation of ziprasidone base of formula (I). The solution of this problem has as special technical feature, the coupling reaction of the compounds II and III according to claim 1 in water in the absence of a base.

The second proposed problem is the provision of an alternative process for the preparation of substantially pure ziprasidone base. The solution of this problem has as special technical feature, the measures of claim 5 namely the obtention of a suspension of ziprasidone in one or more solvents, heating the suspension and recovering the product.

The third proposed problem is the provision of an alternative process for the preparation of substantially pure ziprasidone hydrochloride as well as pharmaceutical composition and uses thereof.
The solution of this problem has as special technical feature, the measures of claim 22, namely the obtention of a suspension of ziprasidone, contacting the suspension with hydrogen chloride to form a solid and isolation of the product.

None of the abovementioned 3 processes have the same or an equivalent special technical feature and due to the fact that no other technical features can be regarded as special technical features in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 3 inventions claimed in the present application in the sense of rule 13.1 PCT.

Re Item V.

A: Invention 1 (subject-matter of claims 1-4)

D1 : US 4 831 031 A (LOWE, III ET AL) 16 May 1989 (1989-05-16)

D2 : US 5 338 846 A (BUSCH ET AL) 16 August 1994 (1994-08-16)
D3 : EP 0 584 903 A (PFIZER INC) 2 March 1994 (1994-03-02)
D4 : US 6 150 366 A (ARENSON ET AL) 21 November 2000 (2000-11-21)

2. Novelty

Documents D1-D3 are considered to represent equally the closest prior art, because these documents also disclose the preparation of ziprasidone base by a coupling reaction of a compound of formula (II) with a 1-(1,2-benzisothiazol-3-yl)piperazine of formula (III) according to present claim 1. However there is no indication in D1-D3, that the coupling reaction could also be carried out in water in absence of a base.
Document D4 refers to compositions comprising crystalline ziprasidone free base. A process for the preparation of ziprasidone base is not disclosed in D4.
The subject-matter of claims 1-4 is therefore novel (Article 33(2) PCT).

3. Inventive step

Starting from the teaching of the closest prior art D1-D3 and according to the present description (see especially p. 2, l. 23 to p. 3, l. 4), the problem to be solved by the present invention may be regarded as the provision of an improved process for the preparation of ziprasidone base (higher purity).
In view of the examples 1-3 it is credible that the problem as defined above has actually been solved by the technical measures of the claimed process.
For a skilled person, in view of the teaching of the prior art documents D1-D3 it was not foreseeable that the coupling reaction of compound (II) and compound (III, as free amine) in water and in absence of a base would give ziprasidone base in higher purity.
Claims 1-4 meet therefore the criteria of Art. 33 (3) PCT.

B: Invention 2 (subject-matter of claims 5-21)

1. Reference is made to the following documents:

D5: WO 03/070246 A (PFIZER PRODUCTS INC) 28 August 2003
D6: US-A-6 110 918 (BUSCH ET AL) 29 August 2000

D7: EP-A-0 965 343 (PFIZER PRODUCTS INC) 22 December 1999
D8: WO 2004/089948 A (HETERO DRUGS LIMITED) 21 October 2004
D9: WO 2004/050655 A (DR. REDDY'S LABORATORIES LTD) 17 June 2004
D10: WO 2005/016325 A (TEVA PHARM. IND. LTD) 24 February 2005

It is pointed out that documents D8-D10 cited with the P category will not be considered in the present examination. It is expected that the claimed priority of the present application is valid (see EPO, J.O. 11/2001, p. 539-542, point 13).

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 5, 6, 8, 12-14,17-21 is in view of the technical teaching of D5-D7 not new in the sense of Article 33(2) PCT.

D5-D7 refer also to a process for the preparation of substantially pure ziprasidone base comprising the obtention of a suspension of ziprasidone in one or more solvents, a heating step and the recovering step of the product by the removal of the solvent (see especially the passages cited in the search respectively).

It is pointed out that the purity as such is not a distinguishing product feature. In other words a known compound is made available to the public at all level of purity. Consequently the documents D5-D7 destroy the novelty of the subject-matter of claims 20-21. Moreover it is pointed out that pure ziprasidone base can be obtained by conventional purification methods.

3. Inventive step

In view of the teaching of the prior art documents D5-D7, which are considered to reprsent equally the closest prior art, the problem to be solved by the present invention may be regarded as the provision of an alternative process for the preparation of substantially pure ziprasidone base.
The measures of dependent claims 7, 9-11, 15 and 16 are merely several straightforward possibilities from which the skilled person would select, in accordance with circumstances,

without the exercise of inventive skill, in order to solve the problem posed.

Consequently, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 7, 9-11, 15 and 16 does not involve an inventive step in the sense of Article 33(3) PCT.

C: Invention 3 (subject-matter of claims 22-31)

1. Reference is made to the following documents:

D5: WO 03/070246 A (PFIZER PRODUCTS INC) 28 August 2003
D7: EP-A-0 965 343 (PFIZER PRODUCTS INC) 22 December 1999
D8: WO 2004/089948 A (HETERO DRUGS LIMITED) 21 October 2004
D9: WO 2004/050655 A (DR. REDDY'S LABORATORIES LTD) 17 June 2004
D10: WO 2005/016325 A (TEVA PHARM. IND. LTD) 24 February 2005
D11: EP-A-0 586 191 (PFIZER INC.) 09 March 1994

It is pointed out that documents D8-D10 cited with the P category will not be considered in the present examination. It is expected that the claimed priority of the present application is valid (see EPO, J.O. 11/2001, p. 539-542, point 13).

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 22-31 is in view of the technical teaching of D5, D7 and D11 not new in the sense of Article 33(2) PCT.

D5, D7 and D11 refer also to a process for the preparation of substantially pure ziprasidone hydrochloride comprising the obtention of a suspension of ziprasidone in one or more solvents, contacting said suspension with hydrogen chloride to form a solide and the recovering step of the product (see especially the passages cited in the search

respectively).

It is pointed out that the purity as such is not a distinguishing product feature. In other words a known compound is made available to the public at all level of purity. Consequently the documents D5, D7 and D11 destroy the novelty of the subject-matter of claims 28-31. Moreover it is pointed out that pure ziprasidone hydrochloride can be obtained by conventional purification methods.